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09/485,245	03/27/2000	ALISON HOPKINS	28911/36128	1697

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MARSHALL O'TOOLE GERSTEIN
MURRAY & BORUN
6300 SEARS TOWER
233 SOUTH WACKER DRIVE
CHICAGO, IL 60606-6402

EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/485,245	HOPKINS, ALISON	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/25/2007 has been entered.

2. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). Claims 1-6 have been canceled. Claims 7-14 are pending and addressed in this Office action.

Previous Rejection

The prior art rejection under 35 USC 103(a) directed to claims 7-14 is maintained. The new matter rejection under 35 USC 112 first paragraph directed to claims 7-10 is maintained.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Once again, claims 7-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godiska et al. (5,759804, filed November 17, 1993) in view of Shen et al. (EP 0 726 310 A1 February 09, 1996). Regarding claims 7-14, Godiska et al teach a method comprising a random mixture of oligonucleotides which are 6-mers, wherein the composition further contains at least a supply of nucleotides for chain extension, a labeled nucleotide, and a polymerase enzyme (col. 8, lines 27-31). Godiska et al differs from the instant invention in that Godiska et al do not expressly teach wherein the solution comprising the random mixture of 6-mers is in a freeze-dried state. Shen et al teach a method and composition similar to that of Godiska et al, wherein said composition is present in a dry state (page 4, lines 37-41). Shen et al teach wherein the composition may comprise primers, a polymerase enzyme, a supply of nucleotides for chain extension, and a stabilizer (page 6, lines 3-7 and 22). Shen et al teach that the composition present in the dry state is advantageous because the composition is stable for a prolonged period, even when stored at high temperature. Shen et al further teach that a composition in a dried state is useful in shipping and storage of commercial preparations for use in e.g., nucleic acid amplification kits (page 6, lines 39-41). Therefore, it would have been *prima facie* obvious to one of ordinary

skill in the art at the time the claimed invention was made to have been motivated to have provided the random mixture of 6-mers in the method as taught by Godiska et al in a dried state for the advantage taught by Shen et al that a nucleic acid composition (such as primers) present in a dried state is useful in shipping and storage of commercial preparations due its increase stability, even when stored for prolonged periods or when stored at high temperatures.

Applicant's traversal

5. Applicant traverses the rejection on the following ground: Applicant states that the application Examples demonstrate a critical and unexpected difference in self-priming activity and labeling intensity between 6-8 mers and 9-mers and there is no teaching in the art that such a difference could occur. Applicant states accordingly, the obviousness rejection should be withdrawn because the art fails to teach the desirability of short primers in a dried primer system or that 6-mer to 8-mers would behave differently with respect to self-priming activity and labeling intensity than do 9-mers. Applicant states that more specifically, Godiska discloses liquid 6-mers but fails to teach that the selection of 6-mers to 8-mers constitutes a critical range or that short primers would be desirable in a dried primer system. Applicant state while Godiska discloses a random mixture of 6-mers and other ingredients the Examiner acknowledges that Godiska does not teach a labeling composition in a dried state. Applicant states that moreover, there is nothing in Godiska that teaches that the selection of 6-mers to 8-mers is important in either the liquid or freeze-dried state to reduce self- annealing. Applicant states that in fact, self-annealing is not mentioned at all.

Applicant asserts that in addition, Shen discloses 48-mer and 22-mer primers and fail to suggest that dried primers should be shortened or alternatively any reason why the primers of Godiska should be dried. Applicant states that this is because the prior art generally taught that longer primers were preferred because longer primers have higher melting temperatures and are this more specific. Applicant states that moreover, Shen acknowledged that "whether a particular composition will function to preserve biological activity for a particular biologically active material is not a priori predictable and only discloses freeze-drying as an option. Applicant states that the prior art generally taught that longer primers were preferred because longer primers have higher melting temperatures and are thus more specific. Applicants states that like Godiska, Shen does not recognize the potential self annealing problem of dried oligonucleotides used in the art at the time and states that "it should easily be possible to include the amplification primers in the lyophilized preparation...". Applicants state that they were the first to recognize the detrimental side effects of the longer dried primers and discovered that shorter dried primers were advantageous over other primers commonly used in the art. Applicant contends that the person of ordinary skill in the at would not have been motivated to modify the short wet primers of Godiska to the long dry primers of Shen after the reading Godiska and Shen. Applicant states that neither of disclosure refers to the problem of self-annealing, and the art primarily was of the mindset that longer primers were more efficient due to the asserted greater hybridization in the priming reaction. Applicant contends that further, Shen provides a contradictory teaching in stating that one could easily add primers to the annealing

reaction to create a functional priming kit, while also saying that whether a particular composition will maintain biological function after freeze drying is unpredictable. Applicant states that one of ordinary skill in the art would immediately understand which position on freeze drying Shen was advocating. Applicant states that nothing in Shen and Godiska, in conjunction with the prevailing use of longer primers in the art at the time, would lead one of ordinary skill to the present invention. Applicant states that in contrast, the person of ordinary skill in the art would have been motivated to modify the short wet primers of Godiska to the long dry primes of Shen, not to the short dried primers of the invention. Applicant states that because the claimed invention is unobvious over what was taught by the prior art and in use by those of skill in the art at the time of Applicant's invention, the rejection under 35 USC 103(a) should be withdrawn.

Examiner's Response

6. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to Applicant's arguments that the instant invention demonstrates the critical and unexpected differences in self-priming activity and labeling intensity between 6-8 mers and 9 mers, the Examiner maintains that the claims as broadly written do not describe or recite any steps, characteristics or improvements which distinguishes Applicant's invention over the teachings of the prior art. The Examiner agrees with Applicant that the art teaches the use of random primers collections of various lengths in random priming methods and the use of dried primer kits that contain long primers, such as dried 15-17-mers.

However, the examiner disagrees that the instant invention demonstrates a critical difference in self-priming activity and labeling intensity between short dried 6-8 mers which resist self-annealing compared with longer long dried 9-mers and above. In fact, contrary to Applicant arguments, the specification specifically the examples 2 and 3 do not depict any resistance of self-annealing when using primers 6-8 mers in DNA labeling experiments but rather shows a reduction in self-annealing (self-priming). The Example 3 depicts the percent incorporation of 6-mer primers taken from the average of two reactions versus the percent incorporation of 9-mer primers taken from a single experiment. The specification specifically states that "the results obtained in the Example 3 were obtained using wet reagents", but *speculates* that "the conclusion would apply also when dried primers are used" (see specification page 10, lines 8-9). Again, the Example 3 does not depict any resistance to self-annealing or self-priming as argued by Appellant and additionally does not show the criticality of random hexamer versus nanomer in a dried state.

In response to Appellants arguments against the references of Godiska and Shen individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the primary reference of Godiska et al., is cited for its teaching of a method comprising a random mixture of 6-mers oligonucleotide as required by the claims 7, 10, 11 and 14 and reagents for a chain extension assay as required by claims 9 and 13. As stated in the prior Office, Godiska

et al do not expressly teach wherein the 6-mers are in a dried state. However, this limitation is provided in the teachings of the secondary reference by Shen. Shen et al teach a method and composition comprising primers in a dried state and reagents for chain extension as required by claims 7-8, 11 and 12. Shen provides motivation for providing the primer and other reagents required for chain extension in a dry state. Shen et al teach that a composition, comprising primers and reagents in a dried state is advantageous because the composition is stable for a prolonged period, even when stored at high temperature. Shen et al further teach that a composition in a dried state is useful in shipping and storage of commercial preparations for use in e.g., nucleic acid amplification kits (page 6, lines 39-41). Thus, the combined teaching of Godiska et al in view of Shen et al establishes a case of obviousness over the instant invention. MPEP 8th edition states that "[T]he test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference....Rather, the test is what the combined teaching of those references would have suggested to those of ordinary skill in the art " *In re Keller,* 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). See also *In re Sneed*, 710 F.2d 1544, 1550, 218 USPQ 385, 389 (Fed. Cir. 1983) ("[I]t is not necessary that the inventions of the references be physically combinable to render obvious the invention under review."); and *In re Nievelt*, 482 F.2d 965, 179 USPQ 224, 226 (CCPA 1973) ("Combining the teachings of references does not involve an ability to combine their specific structures"). Additionally the Courts have established that "the motivation to combine references does not have to be identical to that of appellant to establish obviousness." See *In re*

Kemps, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996). The Examiner further maintains that the secondary reference of Shen provides motivation and the desirability of providing primers in a freeze-dried state, which would have been obvious to one of ordinary skill in the art at the time of the claimed invention. To reiterate, it would have been *prima facie* obvious to one of ordinary skill in the art to dry the reagents of Godiska as taught by Shen to achieve the advantages of Shen of being useful in shipping and storage of commercial preparation due to increased stability, even when stored for prolonged periods or when stored at high temperatures.

Applicant's arguments are not sufficient to overcome the prior art rejections under 35 USC 103(a). Accordingly, the rejections are maintained.

Claim Rejections - 35 USC § 112 first paragraph: New Matter

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Once again, claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of forming a random mixture of oligonucleotides which is resistant to self-annealing

comprising the steps of selecting a random mixture of oligonucleotides which are 6-mers to 8-mer and drying said mixture. Applicant provides no cited support for the new limitation "oligonucleotides which is resistant" and thus a review of the specification as originally filed does not support or depict what is claimed. While the specification illustrates as a group a reduction in the percent (%) of self-priming when utilizing mixtures of oligonucleotides which are 6-mer to 8mers versus oligonucleotides which are 9-mers, there is no disclosure which illustrates whether or not the reduction in % of self-priming is due to a "selection process" of oligonucleotides having a self annealing resistant property or whether or not the reduction in % self-priming is due to an interaction between the random oligonucleotides or whether or not the reduction in the % of self priming is due the sequences of the oligonucleotides. No support has been found anywhere in the specification which suggests that the oligonucleotides of the invention are "resistant" to self-priming or "resistant" to self-annealing. Therefore, the specification would not have suggested to the skilled artisan that the Applicant was in possession of the claimed invention as of filing date.

Applicant's Traversal

8. Applicant traverses the rejection on the following grounds: Applicant states that the new matter rejection should be withdrawn because the Examiner improperly, and contrary to the teaching of Appellants disclosure implies a standard of absolute inalterability with respect to the term "resistant", which is contrary to the plain meaning and usage of the word. Applicant states that Applicant's Appeal Brief, "resistance" is defined as "force that tends to oppose or retard motion". Applicants states that thus, a

time piece which is "water resistant" is not absolutely impervious to penetration by water; rather it retards or diminishes the damaging effect of moisture. Applicant states that similarly the primers described herein are resistant, but not impervious to self-annealing. Applicant states that the primers herein demonstrated a significant and unexpected retarding of self-annealing compared to the prior art primer. Applicant states that one of ordinary skill in the art reviewing Applicant's specification, including the acknowledged reduction in self-annealing of Applicants' primer composition, would have recognized that such was the intended meaning. Applicant states that the Examiner further asserts that the specification does not describe whether or not the reduction in % self-priming is due to a "selection process" of oligonucleotides having a self-annealing resistant property or whether or not the reduction in % self-priming is due to an interaction between the random oligonucleotides or whether or not the reduction in the % of self-priming is due to the sequences of the oligonucleotides. Applicant states that the mechanism of reduction/resistance of self-priming is not an issue in the claim and therefore the specification need not necessarily describe by what mechanism the reduction is occurring. Applicant states that the specification teaches that the self-annealing of dried 9-mers is due to the property that dried 9-mer oligonucleotides tend to bind to each other, i.e., self-primer, while dried 6-mers do not exhibit this tendency toward self-priming of the 6-mers is due the interaction or lack thereof between the dried 6-mer oligonucleotides. Applicant states this application has described the method by which 6-mers are resistance to self-annealing and the rejection under 35 USC 112 first paragraph should be withdrawn.

Examiner's Response

9. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: Applicant's arguments are acknowledged, however, the Examiner maintains and agrees with Applicant that the instant invention does teach a reduction or diminish or reduction or retardation in self-annealing of 6-mers as claimed in comparison to 9-mers as taught in the instant specification. The Examiner asserts that the instant specification does not support a recitation of primers being resistant to self-annealing. There is no teaching anywhere in the specification, which teach or suggest or even implies that primers described herein are resistant to self-annealing as claimed. In regards to Applicant's comments concerning the mechanism of reduction/resistance of self-priming, it is noted that the Examiner makes this point to further establish that the instant specification does not support any teaching of "resistance of self-annealing". Applicant's arguments are not sufficient to overcome the rejection under 35 USC 112 first paragraph. Accordingly, this rejection is maintained.

Conclusion

10. No claims are allowed. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cynthia Wilder

cbw